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Synthesis of (±) curcuphenol and (±)-β-sesquiphellandrene

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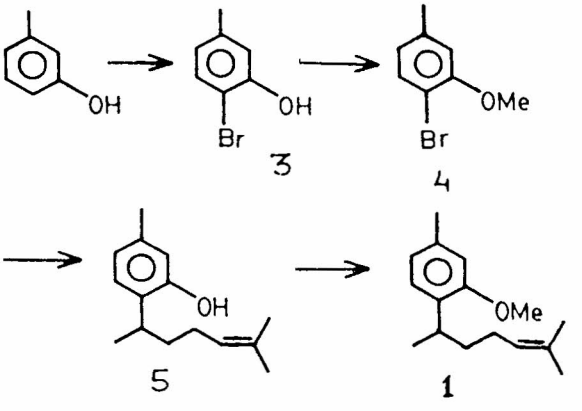
Two naturally occurring compounds curcuphenol **1** and β-sesquiphellandrene **2** have been synthesised using lithium tetrachlorocuperate catalysed coupling reaction.

In continuation[1] of our work on the synthesis of natural products utilizing dilithium tetrachlorocuperate (Li_2CuCl_4) catalysed coupling for the carbon-chain elongation, herein, we report the synthesis of (±)-curcuphenol **1** and (±)-β-sesquiphellandrene **2**.

Wright *et. al.*[2] reported the isolation of sesquiterpene phenol, (+)-curcuphenol, from both deep and shallow water collection of the sponge *Didiscus flavis* Van Soest (Fam. Latrunculizdae). Earlier Fenical and coworkers[3] reported the isolation of (-)-curcuphenol from the metabolite of the gorgonian soft coral *Pseudoptero gorgia* rigida. The isolation [4,5] of (-)-curcuphenol has also been reported from terrestrial plant *Lasiamthaea podocephala*. The isolation of β-sesquiphellandrene was reported by Rodriguez *et.al.*[6] from *Aristolochia chilensis* Miers roots. It was the first report of this compound from a natural source. The structures of both the compounds were assigned on the basis of spectral data. Fenical and coworkers[3] have reported only the synthetic approach to (±)-curcuphenol while no attempt has been made to synthesise β-sesquiphellandrene. Herein, we report a facile synthesis of the compounds **1** and **2** through dilithium tetrachlorocuperate catalysed coupling. The reaction sesquences employed are shown in Scheme I and II.

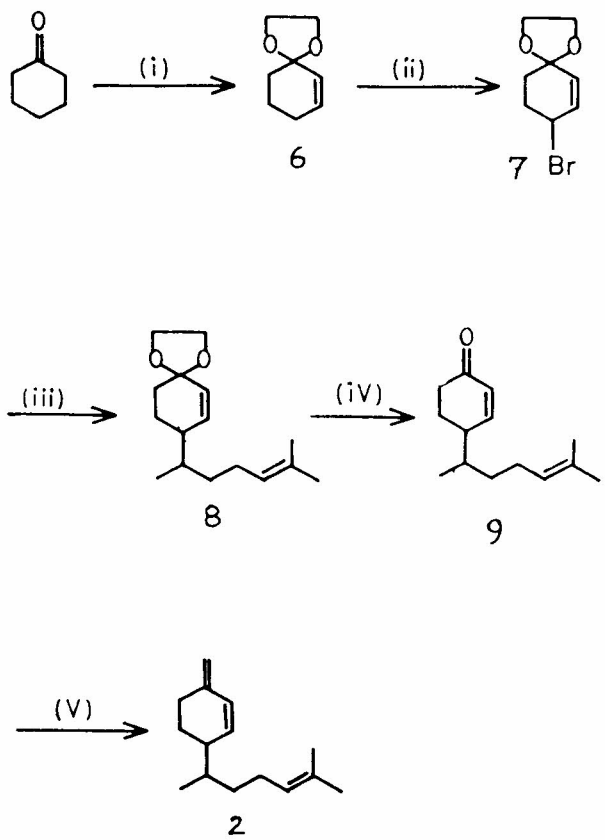
m-Cresol was brominated *ortho*- to hydroxy group by protecting *para*-position with sulphonic acid group followed by deprotection leading to 2-bromo-5-methylphenol **3**. Compound **3** was then methylated with dimethyl suphate in aqueous sodium hydroxide oy irradiating with microwave radiations to get bromoanisole **4**. Grignard reagent prepared from methyl substituted bromoanisole **4** was coupled with 6-bromo-2-methyl-2- heptene[12] using dilithium tetrachlorocuperate[8] as catalyst at -10° to afford methyl curcuphenol **5**, which upon subsequent demethylation[9] with BBr_3 in dichloromethane at -78° furnished the target molecule curcuphenol **1** (Scheme I).

To acheive the target molecule **2**, cyclohexanone was converted[10] into cyclohex-2-enone ethylene ketal **6** which was subsequently brominated[11] at allylic position using NBS in anhydrous CCl_4 to procure 3-bromo-6,6-ethylenedioxycyclohexene **7**. The Grignard reagent prepared from bromide **7** on coupling with 6-bromo-2-methyl-2-heptene[12] using Li_2CuCl_4 as catalyst[8] at -10° in anhydrous THF furnished **8** which was subsequently deketalised to substituted cyclohexenone **9**. Wittig reaction[13] of methyl



Scheme I

†Present Addrress: RDO M/s Himachal Terpene products (p) Ltd. VPO Kala-AMB, Nahan -173030, Distt. Sirmour (HP), India



Scheme II

dimethyl phosphonate with enone **9** using K_2CO_3 as base in refluxing aqueous media afforded the target molecule **2** (Scheme II).

Experimental Section

Boiling points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer ν_{max} in cm^{-1}); ^{1}HNMR spectra in $CDCl_3$ on a Varian EM-390 (90 MHz) spectrometer (chemical shifts in δ, ppm and *J* values in Hz) using TMS as an internal standard; mass spectra on a VG ANALYTICAL 11-250-J 70-S spectrometer at 70 eV. Silica gel (Acme 100-200 mesh) was used for column chromatography. All solvents were dried prior to use employing standard procedures. Unless stated otherwise, the organic extracts were dried over anhydrous sodium sulphate.

2-Bromo-5-methylphenol 5. A strirred mixture of *m*-cresol (32.4g, 0.3mole) and conc. sulphuric acid (84g, 45.6mL) was heated on a boiling water-bath for 2 hr. The reaction mixture was cooled to 10-15°C and then 70g of sodium hydroxide in 175mL of water was slowly added to obtain a solid which later dissolved. The solution was allowed to attain room temperature and to this was added 53g (17mL) of bromine in 45 min. While stirring constantly and maintaining the temperature below 40°C. After the addition of bromine was over, the reaction mixture was further stirred for 1 hr, and then distilled while passing a stream of air. To the remaining thick residue was added 100mL of conc. sulphuric acid alowly while shaking the reaction mixture. The reaction mixture was then heated at 205-10° for 1 hr., cooled and extracted with ether, washed the ethereal layer with water, and dried over anhyd. $MgSO_4$. Evaporation of ether followed by distillation under reduced pressure yielded pure **3** (37.6g, 67%) b.p. 167- 68°/20 mm; IR (KBr) : 3350, 2870, 1645, 1070; ^{1}HNMR: δ2.2 (s, 3H, ArC*H*$_3$, 6.1 (brs, 1H, OH, D_2O exchangeable), 6.73 (d, 1H, aromatic, *J* = 4Hz), 7.03 (s, 1H, aromatic), 7.2 (d, 1H, aromatic, *J* = 7Hz).

2-Bromo-5-methylanisole 4. A mixture of **3** (18.7g, 0.1mole), sodium hydroxide (4.8g, 0.12 mole) and dimethyl sulphate (13.5g, 0.11 mole) in 100mL water was subjected to microwave irradiation at a power level of 9 for 1 min. The contents of the mixture were then cooled, extracted with ether, washed with water and dried. Evaporation of the solvent yielded pure **4** (19.8g, 98.7%); IR (KBr): 2880, 1640, 1070; ^{1}HNMR; δ2.26 (s, 3H, ArC*H*$_3$), 3.73 (s, 3H, OMe), 6.7 (d, 1H, aromatic, *J* = 4 Hz), 7.16 (s, 1H, aromatic), 7.43 (d. 1H, aromatic, *J* = 6 Hz) Found: C, 47.8; H, 4.6. C_8H_9BrO requires C, 47.76; H, 4.47%).

Methyl curcuphenol 5. To an ice-cooled stirred solution of Grignard reagent, prepared from the substituted bromoanisole **4** (4.02g, 0.02 mole) and magnesium turnings (0.504g, 0.021 mole) in THF (70mL) under N_2 atmosphere, was added dropwise a solution of 6-bromo-2-methyl-2-heptene (3.82g, 0.02mole) in THF (50 mL) in about 20 min. The solution was cooled to -10° and then Li_2CuCl_4 (4mL) was added. It was kept at -10° for another 6 hr, and then stirred overnight at room temperature. The reaction mixture was decomposed with saturated solution of NH_4Cl, extracted with ether, washed with water, brine and dried. Evaporation of the solvent followed by chromatographic purification over silica gel using hexane – ether (9.5 : 0.5) as eluent afforded pure **5** (3.68g, 79.4%); IR (KBr): 2920, 2865, 1640, 1035; ^{1}HNMR : δ1.03 (d, 3H, CH_3, *J* = 6Hz), 1.3 (m, 2H), 1.5, 1.6 (2s, 6H, -CH = C(C*H*$_3$)$_2$), 2.1 (m, 2H,

-C*H*$_2$-CH=C), 2.23 (s, 3H, ArC*H*$_3$), 2.4 (m, 1H, CH), 3.9 (s, 3H, OMe), 5.36 (t, 1H, olefinic, *J*=7Hz), 7.03 (d, 1H, aromatic, *J*=7Hz), 7.1 (s, 1H, aromatic), 7.3 (d, 1H, aromatic, *J*=6Hz); ^{13}CNMR : 16.1, 20.2, 21.6, 25.6, 26.1, 31.8, 37.4, 60.5, 115.8, 121.6, 124.9, 126.9, 131.2, 133, 135.6, 153.7; MS : 232 [M]$^+$, 189, 156, 137, 110, 105, 95, 91, 79, 77, 69, 67, 57, 55 (Found: C, 82.8; H, 10.3. $C_{16}H_{24}O$ requires C, 82.75; H, 10.35%).

Curcuphenol 1. To a stirred solution of **5** (0.58g, 2.5moles) in anhydrous CH_2Cl_2 (15mL) at -78° was added BBr_3 (0.65g, 2.6mmoles). The reaction mixture was allowed to attain room temperature and then decomposed with water (2mL), extracted the contents with ether and dried. Evaporation of the solvent furnished pure curcuphenol **1** (0.53g, 96.7%); IR(KBr) : 3340, 1635, 1070; ^{1}HNMR : δ1.2 (d, 3H, *J* = 6.5Hz), 1.6 (m, 2H), 1.53, (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.96 (m, 2H, CH_2), 2.2 (s, 3H, CH_3), 2.86 (m, 1H, CH), 5.13 (t, 1H, *J* = 7Hz), 5.3 (brs, 1H, OH, D_2O exchangeable), 6.86 (s, 1H, aromatic), 7.03 (d, 1H, aromatic, *J* = 7Hz), 7.13 (d, 1H, aromatic, *J* = 8Hz); MS: 218 [M]$^+$, 149, 135, 121, 115, 109, 107, 105, 95, 91, 79, 77, 69, 67, 65, 55; ^{13}CNMR: 16.7, 20.2, 21.6, 25.7, 26.1, 31.9, 37.2, 115.8, 122.1, 123.7, 126.9, 130.8, 131.5, 137.6, 151.5.

Cyclohex-2-enone ethylene ketal 6. Cyclohexanone was converted to cyclohex-2-enone ethylene ketal by standard procedure as reported in the literature[10].

3-Bromo-6, 6-ethylenedioxycyclohexene 7 . The compound **6** (2.8g, 30 mmoles) and NBS (0.18g, 10 mmoles) in anhydrous CCl_4 (50 mL) containing catalytic amount of benzoyl peroxide were heated to 50° slowly to avoid a vigorous reaction. After heating for 2 hr when whole of the solid component started floating over organic layer, the reaction mixture was cooled and filtered. Evaporation of the solvent followed by distillation under diminished pressure yielded pure **7** (5.38g, 82%), b.p. 92- 93°C/15 mm; IR (KBr) : 2920, 1620, 1050, 480; ^{1}HNMR; δ1.9 (m, 4H, 2× CH_2), 4.1 (s, 4H, -OC*H*$_2$C*H*$_2$O-), 4.23 (m, 1H, -CHBr), 6.86 (d, 1H, -C*H*=CH-CHBr, *J*=9Hz), 7.13 (m, 1H, -CH=C*H*-CHBr); MS : 203 [M$^+$], 123, 63, 60 (Found : C, 47.3; H, 5.43; Br, 39.4. $C_8H_{11}BrO$ requires C, 47.29; H, 5.4; Br, 39.4%).

4-(1,5-Dimethyl-4-hexene) cyclohex-2-enone ethylene ketal 8. To a solution of the Grignard reagent prepared from Mg turnings (0.24g, 10 mmoles) and the bromide **8** (2.19g, 10 mmoles) in THF (30 mL) in N_2 atmosphere, was added dropwise a solution of 6- bromo-2-methyl-2-heptene (1.91g, 10 mmoles) in THF (20mL) in 10 min. After stirring for 30 min, Li_2CuCl_4 (2mL) was added. The reaction mixture was stirred for 4 hr at -10° and then stirred for 6hr at room temperature. It was decomposed with saturated solution of NH_4Cl, extracted with ether, washed with water, brine and dried. Evaporation of the solvent followed by chromatographic purification using hexane-ethyl acetate (9.5 :0.5) as eluent yielded pure **8** (1.48g, 59%) ; IR(KBr) : 2990, 1635, 1240, 1070, 730; ^{1}HNMR : δ1.03 (d, 3H, methyl, *J=6.3Hz), 1.36 (m, 2H,* C*H*$_2$), 1.5, 1.6 (2s, 6H, -CH=C(C*H*$_3$)$_2$), 1.9 (brs, 4H, cyclic 2×C*H*$_2$), 2.3 (m, 2H, allylic C*H*$_2$), 2.6 (m, 1H, allylic C*H*, 4.1 (s, 4H, -OC*H*$_2$C*H*$_2$O-), 5.3 (t, 1H, olefinic, *J* = 7Hz), 6.2 (s, 1H, olefinic), 6.53 (dd, 1H, olefinic, *J* = 9.3Hz); MS:250 [M$^+$], 208, 167, 139, 190, 206, 69, 42 (Found : C, 76.9; H, 10.3. $C_{16}H_{26}O_2$ requires C, 76.8; H, 10.4%).

4-(1,5-Dimethyl-4-hexene)cyclohex-2-enone 9. Compound **8** (2.5g, 10 mmoles) was stirred with 10% HCl (40mL) in acetone (80mL) for 2 hr. The progress of the reaction was monitored on TLC. The reaction mixture was then diluted with water (100mL), extracted with ether (50mL), washed with water, brine and dried. Evaporation of the solvent followed by chromatographic purification over silica gel using hexane-ether (9.5 : 0.5) as eluent afforded pure **9** (1.63g, 79%); IR (KBr) : 2970, 1690, 1635, 1410, 1070, 980, 730; ^{1}HNMR : δ1.06 (d, 3H, CH_3, *J* = 6Hz), 1.33 (m, 2H, CH_2), 1.5, 1.6 (2s, 6H, -CH = C(C*H*$_3$)$_2$), 1.9 (m, 2H, cyclic C*H*$_2$), 2.16 (m, 2H, allylic C*H*$_2$), 2.36 (t, 2H, -CH_2CO-, *J* = 6.9Hz), 2.6 (m, 1H, allylic C*H*), 5.3 (t, 1H, olefinic, *J* =7Hz), 6.9 (brs, 1H), 7.03 (m, 1H), MS : 206 [M$^+$], 190, 111, 164, 56, 42 (Found : C, 81.6; H, 10.7. $C_{14}H_{22}O$ requires C, 81.55; H, 10.68%).

β-sesquiphellandrene 1. A mixture of **9** (2.47g, 12 m moles), K_2CO_3 (4.14g, 30 mmoles), methyl dimethyl phosphonate (1.86g, 15 mmoles), and water (30 mL) was refluxed for 4 hr. The reaction mixture was then diluted with water, extracted with ether, washed the ethereal layer with brine and dried ($MgSO_4$). Evaporation of solvent followed by chromatographic purification over neutral alumina with hexane-ether (9 :1) as eluent afforded pure **1** (1.91g, 78%); IR(KBr) : 2970, 1640, 1210, 730, 870; ^{1}HNMR: δ1.03 (d, 3H, CH_3, *J* = 6Hz), 1.39 (m, 2H, CH_2), 1.5, 1.6 (2s, 6H, -CH = C(C*H*$_3$)$_2$), 1.89 (brs,

4H, cyclic 2×CH_2), 2.3 (m, J = 7Hz), 5.7 (d, 1H, olefinic CH_2, J=7Hz), 5.93 (d, 1H, olefinic CH_2 J = 6.6Hz), 6.1(brs, 1H, olefinic), 6.33 (dd, 1H, olefinic, J = 9, 3Hz); MS : 204 [M^+], 192, 156, 111, 56, 42.

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